X^2 for each occurrence is independently hydrogen, optionally substituted $(C_1\text{-}C_6)$alkyl, or optionally substituted $(C_3\text{-}C_7)$cycloalkyl, where the optionally substituted $(C_1\text{-}C_6)$alkyl and optionally substituted $(C_3\text{-}C_7)$cycloalkyl in the definition of X^2 are optionally independently substituted with $-S(O)_m(C_1\text{-}C_6)$alkyl, $-C(O)OX^3$, 1 to 5 halogens or 1-3 OX^3;

X^3 for each occurrence is independently hydrogen or $(C_1\text{-}C_6)$alkyl;

X^6 is independently hydrogen, optionally substituted $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$halogenated alkyl, optionally substituted $(C_3\text{-}C_7)$cycloalkyl, $(C_3\text{-}C_7)$-halogenatedcycloalkyl, where optionally substituted $(C_1\text{-}C_6)$alkyl and optionally substituted $(C_3\text{-}C_7)$cycloalkyl in the definition of X^6 is optionally independently substituted by 1 or 2 $(C_1\text{-}C_4)$alkyl, hydroxyl, $(C_1\text{-}C_4)$alkoxy, carboxyl, $CONH_2$, $-S(O)_m(C_1\text{-}C_6)$alkyl, carboxylate $(C_1\text{-}C_4)$alkyl ester, or 1H-tetrazol-5-yl; or

when there are two X^6 groups on one atom and both X^6 are independently $(C_1\text{-}C_6)$alkyl, the two $(C_1\text{-}C_6)$alkyl groups may be optionally joined and, together with the atom to which the two X^6 groups are attached, form a 4- to 9- membered ring optionally having oxygen, sulfur or NX^7;

X^7 is hydrogen or $(C_1\text{-}C_6)$alkyl optionally substituted with hydroxyl; and

m for each occurrence is independently 0, 1 or 2;

with the proviso that:

X^6 and X^{12} cannot be hydrogen when it is attached to C(O) or SO_2 in the form $C(O)X^6$, $C(O)X^{12}$, SO_2X^6 or SO_2X^{12}; and

when R^6 is a bond then L is $N(X^2)$ and each r in the definition $-(CH_2)_r\text{-}L\text{-}(CH_2)_r-$ is independently 2 or 3.

REMARKS

The present invention is directed to a method for improving the functional health status of an individual, that has been detrimentally impacted by age. This may be accomplished by administering to the individual a growth hormone secretagogue. Claims 1-12, 15-21, and 26-38 remain pending. Claims 13 and 14 have been cancelled in view of the amendment to claim 1 above. Non-elected claims 22-25 have been cancelled.

Claim 1 has been amended to further distinguish the claims from the prior art. Claim 1 is directed to a method for improving the functional health status of a patient, where age has adversely impacted that individual. Support for such an amendment may be found on page 30 of the specification, at line 11.

Claim 19 was objected to due to a typographical error. Y has been changed to Y^2, as requested. It is respectfully requested that the rejection of record be withdrawn in light of the comments below

REJECTION UNDER 35 USC 103

Claims 1-21 and 26-38 (hereinafter the claims) were rejected under 35 USC 103 in light of WO 97/41879 or WO0012047, when combined with WO 97/24369. The gist of the USPTO's rejection is: 1) the '047 application discloses using growth hormone secretogues ("GHS") to enhance the rate at which individuals suffering traumatic injury resume independent living status; 2) the '369 application teaches that the elected compound has GHS activity; and 3), it would be obvious to use GHS to improve the functional status of an individual, since returning that individual to independent living status would necessarily require an improvement in their health status. Further, the '879 application discloses the use of GHS to enhance sleep and thus would further contribute to improving functional status.

It is respectfully submitted that the amendment to claim 1 distinguishes the claims from the prior art and that the rejection should be withdrawn. Claim 1, as amended, is directed to a method for improving the functional health status of a patient, whose physical performance has declined as the result of age, not as the result of trauma or disease. As is discussed on page 30 of Applicants' specification, elderly individuals often have normal growth hormone levels, but suffer from symptoms typically associated with abnormally low growth hormone levels.

As is further discussed beginning at page 30, line 11, these symptoms have an adverse effect on the physical performance of the individual. For example, as discussed on page 30, at line 29, the elderly often have decreases in hand strength, gait speed, chair rise time, etc. Decreases in these skills often lead to the necessity of assisted living arrangements, such as nursing homes. This diminished performance is the result of age, not trauma.

One of the USPTO's primary references, the '047 application, is directed to an entirely different group of individuals. It is directed to patients who have suffered physical injuries such as broken bones, burns, gunshot wounds, or have undergone major surgery, etc. The patient may be elderly, middle aged or young. Regardless of age, the physical trauma has produced muscular atrophy, which has diminished the patients capacity to live unassisted. The '047 application teaches that GHS will enhance protein synthesis in these patients, reduce muscular atrophy, and thereby enhance the rate at which the patient can live without assistance.

The other primary reference, the '879 application, is also directed to a different group of patients. The '879 application discloses that GHS can be used to treat sleep disorders. Patients with sleep disorders include those suffering from jet lag and workers on rotating shifts. Neither group brings to mind the elderly, as required by amended claim 1. The '879 application also teaches that GHS can be used to treat sleep disturbances associated with chronic diseases such as narcolepsy, sleep apnea, etc.

The USPTO asserts that "one skilled in the pharmaceutical arts would be motivated to practice the claimed invention since the claimed attributes relate to outcomes achieved by practicing the methods of the primary references." It is respectfully submitted that the USPTO

is using the wrong analysis. To be obvious, one of ordinary skill in the art would need a reasonable expectation of success. Motivation to practice, is analogous to motivation to try, which the CAFC has repeatedly stated is not the proper test for determining obviousness.

Further, the primary references do not provide an expectation of success. Claim 1 requires the GHS to be administered to an elderly individual who is suffering from the effects of old age, not an acute injury, as required by the '047 application. The '047 application discloses that GHS's impact on protein synthesis leads to enhanced healing and increased rates of unassisted living. Nothing in the '047 application would lead one to expect that GHS could reverse the ravages of age.

The same analysis is relevant to the '879 application. It discloses the use of GHS for sleep disturbances. Many of these disturbances are the result of active disease processes whose etiologies are not well understood. Examples include narcolepsy, sleep apnea, etc. There is no causal link between aging and narcolepsy for example. A disclosure that a substance will alleviate narcolepsy would not provide an expectation of success that the same class of molecules could be used to help diminish the effects of aging.

Withdrawal of the rejection of record and reconsideration is respectfully requested.

Respectfully submitted,

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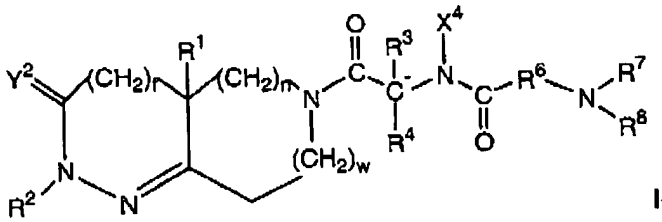
VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. A method for improving functional health status in a patient with age-related decline in physical performance ~~in need thereof~~ which comprises administering to the patient a therapeutically effective amount of a growth hormone secretagogue.

19. A method of claim 18 wherein the growth hormone secretagogue is a compound of Formula I-A



I-A

a racemic-diastereomeric mixture or an optical isomer of said compound or a pharmaceutically-acceptable salt or a prodrug thereof, or a tautomer thereof,
wherein

f is 0;

n is 0 and w is 2, or n is 1 and w is 1, or n is 2 and w is 0;

Y^2 is oxygen or sulfur;

R^1 is hydrogen, -CN, $-(CH_2)_qN(X^6)C(O)X^6$, $-(CH_2)_qN(X^6)C(O)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)SO_2(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)SO_2X^6$, $-(CH_2)_qN(X^6)C(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)C(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qC(O)OX^6$, $-(CH_2)_qC(O)O(CH_2)_t-A^1$, $-(CH_2)_qOX^6$, $-(CH_2)_qOC(O)X^6$, $-(CH_2)_qOC(O)(CH_2)_t-A^1$, $-(CH_2)_qOC(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qOC(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)X^6$, $-(CH_2)_qC(O)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)C(O)OX^6$, $-(CH_2)_qN(X^6)SO_2N(X^6)(X^6)$, $-(CH_2)_qS(O)_mX^6$, $-(CH_2)_qS(O)_m(CH_2)_t-A^1$, $-(C_1-C_{10})$alkyl, $-(CH_2)_t-A^1$, $-(CH_2)_q-(C_3-C_7)$cycloalkyl, $-(CH_2)_q-Y^1-(C_1-C_6)$alkyl, $-(CH_2)_q-Y^1-(CH_2)_t-A^1$ or $-(CH_2)_q-Y^1-(CH_2)_t-(C_3-C_7)$cycloalkyl;

where the alkyl and cycloalkyl groups in the definition of R^1 are optionally substituted with (C_1-C_4)alkyl, hydroxyl, (C_1-C_4)alkoxy, carboxyl, $-CONH_2$, $-S(O)_m(C_1-C_6)$alkyl, $-CO_2(C_1-C_4)$alkyl ester, 1H-tetrazol-5-yl or 1, 2 or 3 fluoro;

Y^1 is O, $S(O)_m$, $-C(O)NX^6-$, -CH=CH-, -C≡C-, $-N(X^6)C(O)-$, -C(O)O-, $-OC(O)N(X^6)-$ or -OC(O)-;

q is 0, 1, 2, 3 or 4;

t is 0, 1, 2 or 3;

said $(CH_2)_q$ group and $(CH_2)_t$ group may each be optionally substituted with hydroxyl, (C_1-C_4)alkoxy, carboxyl, $-CONH_2$, $-S(O)_m(C_1-C_6)$alkyl, $-CO_2(C_1-C_4)$alkyl ester, 1H-tetrazol-5-yl, 1, 2 or 3 fluoro, or 1 or 2 (C_1-C_4)alkyl;

R^2 is hydrogen, (C_1-C_8)alkyl, $-(C_0-C_3)$alkyl-(C_3-C_8)cycloalkyl, $-(C_1-C_4)$alkyl-A^1 or A^1;

where the alkyl groups and the cycloalkyl groups in the definition of R^2 are optionally substituted with hydroxyl, $-C(O)OX^6$, $-C(O)N(X^6)(X^6)$, $-N(X^6)(X^6)$, $-S(O)_m(C_1-C_6)$alkyl, $-C(O)A^1$, $-C(O)(X^6)$, CF_3, CN or 1, 2 or 3 halogen;

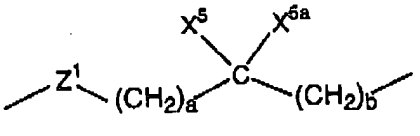
R^3 is A^1, (C_1-C_{10})alkyl, $-(C_1-C_6)$alkyl-A^1, $-(C_1-C_6)$alkyl-(C_3-C_7)cycloalkyl, $-(C_1-C_5)$alkyl-X^1-(C_1-C_5)alkyl, $-(C_1-C_5)$alkyl-X^1-(C_0-C_5)alkyl-A^1 or $-(C_1-C_5)$alkyl-X^1-(C_1-C_5)alkyl-(C_3-C_7)cycloalkyl;

where the alkyl groups in the definition of R^3 are optionally substituted with, $-S(O)_m(C_1-C_6)$alkyl, $-C(O)OX^3$, 1, 2, 3, 4 or 5 halogens, or 1, 2 or 3 OX^3;

X^1 is O, $S(O)_m$, $-N(X^2)C(O)-$, $-C(O)N(X^2)-$, $-OC(O)-$, $-C(O)O-$, $-CX^2=CX^2-$, $-N(X^2)C(O)O-$, $-OC(O)N(X^2)-$ or $-C\equiv C-$;

R^4 is hydrogen, (C_1-C_6)alkyl or (C_3-C_7)cycloalkyl;

X^4 is hydrogen or (C_1-C_6)alkyl or X^4 is taken together with R^4 and the nitrogen atom to which X^4 is attached and the carbon atom to which R^4 is attached and form a five to seven membered ring;

R^6 is a bond or is  ;

where a and b are independently 0, 1, 2 or 3;

X^5 and X^{5a} are each independently selected from the group consisting of hydrogen, trifluoromethyl, A^1 and optionally substituted (C_1-C_6)alkyl;

the optionally substituted (C_1-C_6)alkyl in the definition of X^5 and X^{5a} is optionally substituted with a substituent selected from the group consisting of A^1, OX^2, $-S(O)_m(C_1-C_6)$alkyl, $-C(O)OX^2$, (C_3-C_7)cycloalkyl, $-N(X^2)(X^2)$ and $-C(O)N(X^2)(X^2)$;

R^7 and R^8 are independently hydrogen or optionally substituted (C_1-C_6)alkyl;

where the optionally substituted (C_1-C_6)alkyl in the definition of R^7 and R^8 is optionally independently substituted with A^1, -C(O)O-(C_1-C_6)alkyl, -S(O)$_m$(C_1-C_6)alkyl, 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 -O-C(O)(C_1-C_{10})alkyl or 1 to 3 (C_1-C_6)alkoxy; or

R^7 and R^8 can be taken together to form -$(CH_2)_r$-L-$(CH_2)_r$-;

where L is $C(X^2)(X^2)$, $S(O)_m$ or $N(X^2)$;

A^1 in the definition of R^1 is a partially saturated, fully saturated or fully unsaturated 4- to 8-membered ring optionally having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, a bicyclic ring system consisting of a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

A^1 in the definition of R^2, R^3, R^6, R^7 and R^8 is independently (C_5-C_7)cycloalkenyl, phenyl or a partially saturated, fully saturated or fully unsaturated 4- to 8- membered ring optionally having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, a bicyclic ring system consisting of a partially saturated, fully unsaturated or fully saturated 5- or 6- membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6- membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

A^1 for each occurrence is independently optionally substituted, in one or optionally both rings if A^1 is a bicyclic ring system, with up to three substituents, each substituent independently selected from the group consisting of F, Cl, Br, I, OCF_3, OCF_2H, CF_3, CH_3, OCH_3, -OX^6, -C(O)N(X^6)(X^6), -C(O)OX^6, oxo, (C_1-C_6)alkyl, nitro, cyano, benzyl, -S(O)$_m$(C_1-C_6)alkyl, 1H-tetrazol-5-yl, phenyl, phenoxy, phenylalkyloxy, halophenyl, methylenedioxy, -N(X^6)(X^6), -N(X^6)C(O)(X^6), -SO_2N(X^6)(X^6), -N(X^6)SO_2-phenyl, -N(X^6)SO_2X^6, -CON$X^{11}X^{12}$, -$SO_2NX^{11}X^{12}$, -$NX^6SO_2X^{12}$,

$-NX^6CONX^{11}X^{12}$, $-NX^6SO_2NX^{11}X^{12}$, $-NX^6C(O)X^{12}$, imidazolyl, thiazolyl or tetrazolyl, provided that if A^1 is optionally substituted with methylenedioxy then it can only be substituted with one methylenedioxy;

where X^{11} is hydrogen or optionally substituted $(C_1\text{-}C_6)$alkyl;

the optionally substituted $(C_1\text{-}C_6)$alkyl defined for X^{11} is optionally independently substituted with phenyl, phenoxy, $(C_1\text{-}C_6)$alkoxycarbonyl, $-S(O)_m(C_1\text{-}C_6)$alkyl 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 $(C_1\text{-}C_{10})$alkanoyloxy or 1 to 3 $(C_1\text{-}C_6)$alkoxy;

X^{12} is hydrogen, $(C_1\text{-}C_6)$alkyl, phenyl, thiazolyl, imidazolyl, furyl or thienyl, provided that when X^{12} is not hydrogen, X^{12} is optionally substituted with one to three substituents independently selected from the group consisting of Cl, F, CH_3, OCH_3, OCF_3 and CF_3;

or X^{11} and X^{12} are taken together to form $-(CH_2)_r\text{-}L^1\text{-}(CH_2)_r$-;

where L^1 is $C(X^2)(X^2)$, O, $S(O)_m$ or $N(X^2)$;

r for each occurrence is independently 1, 2 or 3;

X^2 for each occurrence is independently hydrogen, optionally substituted $(C_1\text{-}C_6)$alkyl, or optionally substituted $(C_3\text{-}C_7)$cycloalkyl, where the optionally substituted $(C_1\text{-}C_6)$alkyl and optionally substituted $(C_3\text{-}C_7)$cycloalkyl in the definition of X^2 are optionally independently substituted with $-S(O)_m(C_1\text{-}C_6)$alkyl, $-C(O)OX^3$, 1 to 5 halogens or 1-3 OX^3;

X^3 for each occurrence is independently hydrogen or $(C_1\text{-}C_6)$alkyl;

X^6 is independently hydrogen, optionally substituted $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$halogenated alkyl, optionally substituted $(C_3\text{-}C_7)$cycloalkyl, $(C_3\text{-}C_7)$-halogenatedcycloalkyl, where optionally substituted $(C_1\text{-}C_6)$alkyl and optionally substituted $(C_3\text{-}C_7)$cycloalkyl in the definition of X^6 is optionally independently substituted by 1 or 2 $(C_1\text{-}C_4)$alkyl, hydroxyl, $(C_1\text{-}C_4)$alkoxy, carboxyl, $CONH_2$, $-S(O)_m(C_1\text{-}C_6)$alkyl, carboxylate $(C_1\text{-}C_4)$alkyl ester, or 1H-tetrazol-5-yl; or

when there are two X^6 groups on one atom and both X^6 are independently $(C_1\text{-}C_6)$alkyl, the two $(C_1\text{-}C_6)$alkyl groups may be optionally joined and, together with the atom to which the two X^6 groups are attached, form a 4- to 9- membered ring optionally having oxygen, sulfur or NX^7;

X^7 is hydrogen or $(C_1\text{-}C_6)$alkyl optionally substituted with hydroxyl; and

m for each occurrence is independently 0, 1 or 2;

with the proviso that:

X^6 and X^{12} cannot be hydrogen when it is attached to C(O) or SO_2 in the form $C(O)X^6$, $C(O)X^{12}$, SO_2X^6 or SO_2X^{12}; and

when R^6 is a bond then L is $N(X^2)$ and each r in the definition $-(CH_2)_r-L-(CH_2)_r-$ is independently 2 or 3.

REMARKS

The present invention is directed to a method for improving the functional health status of an individual, that has been detrimentally impacted by age. This may be accomplished by administering to the individual a growth hormone secretagogue. Claims 1-12, 15-21, and 26-38 remain pending. Claims 13 and 14 have been cancelled in view of the amendment to claim 1 above. Non-elected claims 22-25 have been cancelled.

Claim 1 has been amended to further distinguish the claims from the prior art. Claim 1 is directed to a method for improving the functional health status of a patient, where age has adversely impacted that individual. Support for such an amendment may be found on page 30 of the specification, at line 11.

Claim 19 was objected to due to a typographical error. Y has been changed to Y^2, as requested. It is respectfully requested that the rejection of record be withdrawn in light of the comments below

REJECTION UNDER 35 USC 103

Claims 1-21 and 26-38 (hereinafter the claims) were rejected under 35 USC 103 in light of WO 97/41879 or WO0012047, when combined with WO 97/24369. The gist of the USPTO's rejection is: 1) the '047 application discloses using growth hormone secretogues ("GHS") to enhance the rate at which individuals suffering traumatic injury resume independent living status; 2) the '369 application teaches that the elected compound has GHS activity; and 3), it would be obvious to use GHS to improve the functional status of an individual, since returning that individual to independent living status would necessarily require an improvement in their health status. Further, the '879 application discloses the use of GHS to enhance sleep and thus would further contribute to improving functional status.

It is respectfully submitted that the amendment to claim 1 distinguishes the claims from the prior art and that the rejection should be withdrawn. Claim 1, as amended, is directed to a method for improving the functional health status of a patient, whose physical performance has declined as the result of age, not as the result of trauma or disease. As is discussed on page 30 of Applicants' specification, elderly individuals often have normal growth hormone levels, but suffer from symptoms typically associated with abnormally low growth hormone levels.

As is further discussed beginning at page 30, line 11, these symptoms have an adverse effect on the physical performance of the individual. For example, as discussed on page 30, at line 29, the elderly often have decreases in hand strength, gait speed, chair rise time, etc.

Decreases in these skills often lead to the necessity of assisted living arrangements, such as nursing homes. This diminished performance is the result of age, not trauma.

One of the USPTO's primary references, the '047 application, is directed to an entirely different group of individuals. It is directed to patients who have suffered physical injuries such as broken bones, burns, gunshot wounds, or have undergone major surgery, etc. The patient may be elderly, middle aged or young. Regardless of age, the physical trauma has produced muscular atrophy, which has diminished the patients capacity to live unassisted. The '047 application teaches that GHS will enhance protein synthesis in these patients, reduce muscular atrophy, and thereby enhance the rate at which the patient can live without assistance.

The other primary reference, the '879 application, is also directed to a different group of patients. The '879 application discloses that GHS can be used to treat sleep disorders. Patients with sleep disorders include those suffering from jet lag and workers on rotating shifts. Neither group brings to mind the elderly, as required by amended claim 1. The '879 application also teaches that GHS can be used to treat sleep disturbances associated with chronic diseases such as narcolepsy, sleep apnea, etc.

The USPTO asserts that "one skilled in the pharmaceutical arts would be motivated to practice the claimed invention since the claimed attributes relate to outcomes achieved by practicing the methods of the primary references." It is respectfully submitted that the USPTO is using the wrong analysis. To be obvious, one of ordinary skill in the art would need a reasonable expectation of success. Motivation to practice, is analogous to motivation to try, which the CAFC has repeatedly stated is not the proper test for determining obviousness.

Further, the primary references do not provide an expectation of success. Claim 1 requires the GHS to be administered to an elderly individual who is suffering from the effects of old age, not an acute injury, as required by the '047 application. The '047 application discloses that GHS's impact on protein synthesis leads to enhanced healing and increased rates of unassisted living. Nothing in the '047 application would lead one to expect that GHS could reverse the ravages of age.

The same analysis is relevant to the '879 application. It discloses the use of GHS for sleep disturbances. Many of these disturbances are the result of active disease processes whose etiologies are not well understood. Examples include narcolepsy, sleep apnea, etc. There is no causal link between aging and narcolepsy for example. A disclosure that a substance will alleviate narcolepsy would not provide an expectation of success that the same class of molecules could be used to help diminish the effects of aging.

Withdrawal of the rejection of record and reconsideration is respectfully requested.